REMARKS/ARGUMENTS

Claims 5-8 and 51-62 are withdrawn. Claims 16, 35 and 47 are cancelled. Claims 17, 19, 23, 24-26, 42, 43-45, 47, 59 and 60 are amended. New claims 63-66 are added. No new matter is added by these amendments. After this Amendment, claims 1-4, 9-15, 17-34, 36-50 and 63-66 are pending in the application.

Claims 17 and 19 are amended to avoid dependence from canceled claims. Claims 23, 42 and 59 are amended to proper Markush format. Claims 24, 43, 60 are amended to clarify that antigen targets of antibodies are not the same as the antibodies themselves. For example, CC49 antigen is the antigen that is bound by antibody CC49. Similarly, anti-TAC refers to an antibody that binds to the TAC antigen. Claim 34 is amended to correct an obvious grammatical error. Claims 25, 26, 44 and 45 are amended to recite antibodies that were known and readily available to the public. New claims 63-66 have been added to recite specific antibodies that were reported in patent applications prior to the effective filing date of the instant application. Support for the specific antibodies may be found in the Specification and claims as originally filed.

Claim Rejections - 35 USC § 112, second paragraph

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is unclear, according to the Office Action, what the R group could be. The Office Action asserts that although the specification defined the R group to be the side chain of any amino acid, the specification did not "set forth what constitutes any side chain of any amino acid." Applicant respectfully traverses the rejection.

What constitutes a side chain of an amino acid for the R group is well known to one skilled in the art. A review of any standard biology text book will provide a list of the 20 natural amino acids and their side chains. *See* Biology, 5th edition by Campbell, Reece and Mitchell (1999). For example, the R group may be as simple as a hydrogen as in the amino acid glycine or it may be a carbon skeleton with various functional groups attached, as in glutamine. As such, one skilled in the art would be apprised of the scope of claim 32. However, in order to advance prosecution, claim 20 is amended to clarify that "R" may be selected from the known side chains of any of the 20 natural amino acids, as listed in amended claim 32.

Claim Rejections - 35 USC § 112, first paragraph

Claims 25-26, 44 and 46-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because, according to the Office Action, the specification does not provide evidence that the claimed biological materials are known and readily available to the public or reproducible from the written description. Applicant respectfully traverses the rejection and notes that U.S. Patent 5,874,540, issued 2/23/99 reports the amino acid sequence for the monoclonal antibody MN14; U.S. Patent 5,789,554, issued 8/4/98 reports the amino acid sequence for the monoclonal antibody LL2 and the antibody was deposited with the American Type Culture Collection (ATCC) under ATCC Accession No. PTA-6735. U.S. application 2004/0077081 reports that the hybridoma cell line for the G250 monoclonal antibody was deposited at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ) under accession number 2526. Monoclonal antibody CC49 was deposited with the ATCC and was accorded accession number ATCC No. HB 9459 and hybridomas J533 and J591 were deposited on June 6, 1996, and received ATCC numbers HB-12127 and HB-12126, respectively. The monoclonal antibody L243 has been deposited at the ATCC under accession number ATCC HB55.

The antibodies recited in new claims 63-66 are antibodies that were reported prior to the effective filing date of the instant application. Provisional application 60/360,229 filed 3/1/2002 and incorporated by reference in the instant application discloses the RS7 antibody; provisional application 10/116,116 filed 4/5/02, incorporated by reference, discloses the Mu-9 antibody, provisional application 60/388,314 filed 6/14/02, incorporated by reference, discloses the PAM-4 antibody; provisional application 60/360,259 filed 3/1/2002 discloses the LL1 antibody; provisional application 60/339,707, filed 8/1/02 discloses the AFP-31 antibody; and provisional application 60/416,232 filed 10/7/02 discloses the hA20 antibody. These references demonstrate that production and use of these antibodies were known in the art prior to the effective filing date of the instant application (December 13, 2002).

Accordingly, Applicant requests withdrawal of this rejection.

Double Patenting

Claims 1-4, 9-15, 17-34 and 36-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 and 47-62 of copending Application No. 11/388,032.

Applicant requests that the provisional double patenting rejection be held in abeyance until such time as allowable subject matter is indicated in one of the two applications. Until such time, the rejection is "provisional" and is indicated as such in the Official Action. According to MPEP 822.01:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Thus, no further action on applicant's part with respect to the provisional double patenting rejection is required.

Claim Rejections - 35 USC§ 103

Claims 1-4, 9, 11-15, 17, 19, 21-24, 27-31, 33-34, 36, 38, 40-43 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763, 2001) in view of Zhao et al. (US 6,716,821, 2004).

Claims 25 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. in view of Zhao et al. in further view of Newton et al. (Blood 2001; 97: 528-535).

Claims 18, 20, 26, 37, 39, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. in view of Zhao et al. and Newton et al. in further view of Cao et al. (Bioconjugate Chemistry 1998; 9: 635-643).

All of the above rejections are based on the combination of Chari in view of Zhao et al. with the addition of one or two additional references. Therefore, once the impropriety of using Chari in combination with Zhao is established, all of the rejections based on Chari and Zhao must fall.

Chari is cited as teaching "an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population." [Action at page 6] Chari, however, does not make obvious the claims because Chari does not teach or suggest a linker that includes a water solubilizing moiety. In fact, the Office Action acknowledges that "Chari et al. do not explicitly teach that the linker further comprises a water-solubilizing moiety between the therapeutic moiety and the cell binding agent, wherein the water-solubilizing agent is an aminopolycarboxylate such as PEG." [Action at page 7]

Furthermore, Chari reports a combination therapy, where the immunoconjugate is administered either separately or as components of the same composition with a chemotherapeutic agent. In Chari, the immunoconjugate includes a cell binding agent and at least one therapeutic agent for killing cell populations. Chari reports that the therapeutic agent for killing selected a cell population is preferably an anti-mitotic agent such as a maytansinoid, a *Vinca* alkaloid, a dolastatin or a cryptophycin. The chemotherapeutic agent includes taxanes, platinum compounds, epipodophyllotoxins compounds, camptothecin compounds or any combination thereof.

Nowhere does Chari teach or suggest that the immunoconjugate includes a linker with a water solubilizing moiety. As the Office Action acknowledged, Chari also "does not explicitly teach that the anti-mitotic agent is a taxane, doxorubicin and/or analog thereof, or camptothecin, e.g. CPT, and/or analog thereof" as cytotoxic component of the immunoconjugate. [Office Action at pg. 7]

Zhao is cited as teaching "cytotoxic agents bearing a polyethylene glycol (PEG) linking group having a terminal active ester and cytotoxic conjugates comprising one or more cytotoxic agents linked to a cell-binding agent via a PEG linking group."

Nowhere does Zhao teach that the a linker comprise a thiol-reactive functional group for binding to the antibody via a thiol group." Zhao teaches cytotoxic conjugates that are formed

using thiol-containing drugs for binding to the linker, and the latter is attached to a targeting entity by an amide bond.

Moreover, the combination of Chari et al. and Zhao et al. viewed in their entirety would not lead a person of ordinary skill in the art to arrive at the claimed invention. The combination of references the Office Action proposes would require that the solubilizing agent reported in Zhao be used as a part of the linker to link a cell binding agent and a therapeutic agent as reported in Chari et al., and, further, incorporate a chemotherapeutic drug administration to complete the 2-component aspect of the Chari invention. The combination, viewed in its entirety, is unlike the claimed invention.

At a minimum, Chari and Zhao fail to establish a *prima facie* case of obviousness because neither reference alone or in combination teaches or suggests a linker comprising a thiol-reactive functional group for binding to the antibody via a thiol group, a water-solubilizing moiety; and the chemotherapeutic moiety attached via an intracellularly-cleavable moiety other than a hydrazone. Accordingly, Applicant requests withdrawal of the rejection.

In the case of Cao et al., Cao et al. reports to an anti-drug (or toxin) antibody as part of the structure of the bispecific antibody. The cited paragraphs (page 640, 1st column, 2nd & 3rd paragraphs) describe bispecific antibodies with one arm being an anti-drug (methotrexate or doxorubicin) antibody or an anti-toxin (saporin) antibody, and the other arm being specific for a target. One skilled in the art will recognize this as a non-covalent drug (or toxin) combination with the bispecific antibody. The reference clearly teaches away from the covalent drug conjugates of the present application. For one skilled in the art to combine this reference with Chari, one would have to form a *covalent* drug conjugate with the bispecific antibody, leaving the anti-drug (or anti-toxin) antibody arm of the bispecific, meant for *non-covalent* attachment to the drug, useless; and then combine free drug with a covalent immunoconjugate of the bispecific to complete the Chari recitation. There is no motivation, let alone reasonable expectation of success, in this exercise.

Claims 1-4, 9-15, 17-24, 27, 29-43, 48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Firestone et al. (US 6,214,345) in view of Greenwald et al. (US 5,824,701) and Miller et al. (224th ACS National Meeting, Boston, Mass., Poster Presentation)

Claims 25-26, 44-45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Firestone et al. in view of Greenwald et al. and Miller et al. in further view of Newton et al.

All of the above rejections are based on the combination of Firestone et al. in view of Greenwald et al. with the addition of one or two additional references. Therefore, once the impropriety of using Firestone et al. in combination with Greenwald et al. is established, all of the rejections based on Firestone et al. and Greenwald et al. must fall.

Firestone is cited as teaching a drug ligand conjugate and a peptide linker. The Office Action points to the drug ligand conjugate having the formula 1Xb "wherein the antibody is linked to the linker via thiol, the spacer/peptide linker having a reactive functional group with the free thiol of said antibody, e.g., maleimide group, at its N-terminus and a one or more amino acid residues for linkage to the drug." [Action at page 10]

As the Office Action acknowledges, Firestone, does not teach or suggest that the linker includes a water solubilizing moiety as recited in claim 1. [Action at page 11] In addition, Firestone does not specify that intracellularly-cleavable moiety is an ester moiety, cleavable by intracellular esterases, as defined in the claims. These two aspects (absence of an ester moiety and a water-solubilizing moiety) clearly distinguish Firestone from the present application.

Greenwald is cited as teaching "taxane prodrugs having a water soluble PEG derivative." Although Greenwald may report solubilizing a taxane prodrug agent, it does not report an immunoconjugate that includes an antibody, a chemotherapeutic moiety, and a linker comprising a thiol-reactive functional group for binding to the antibody via a thiol group, a water-solubilizing moiety, and the chemotherapeutic moiety attached via an intracellularly-cleavable moiety other than a hydrazone, as recited in claim 1.

Miller *et al.* is cited as providing the requisite motivation to combine Firestone with Greenwald because, according to the Office Action, Miller notes that "one problem associated with antibody-drug conjugate formation is the presence of free drug found in the conjugate as a result of hydrophobic interactions that cause the drug to 'stick' to the antibody such that it compromises the efficiency of the antibody." [Action at page 11-12]

Miller *et al.* do not offer evidence that introducing water solubilizing groups solved the "sticking" problem. As a matter of fact, self association or "stacking" of drugs is a well known

problem even when using highly soluble drugs such as doxorubicin and daunorubicin, or other entities such as proflavin, purine derivatives, and acridine orange. Moreover, free drug from antibody-drug conjugates can be removed by ion-exchange chromatography. Miller's assertion that solubilization would remedy 'sticking' of free drugs is unsubstantiated and without merit and in fact Miller indicates that "as the size of the PEG was increased there was a large increase in water solubility, but this was unfortunately accompanied by a decrease in cytotoxicity." Thus, Miller does not provide the motivation to make the combination, nor the expectation of success upon doing so.

No *prima facie* case of obviousness of claim 1 and claims dependent thereon is supported based upon the combination of the primary reference that teaches the use of immunoconjugates (Firestone) and the secondary references (Greenwald and Miller) that teach the use of solubilizing drugs.

In conclusion, all of the claims remaining in this application should now be seen to be in condition for allowance. A prompt notice to that effect is respectfully solicited. If there are any remaining questions, the Examiner is requested to contact the undersigned at the number listed below.

Respectfully submitted,

By: /Tanya D'Souza/
Tanya S. D'Souza, Reg. No. 56,948
612/766-7835
Customer No.: 35657

Dated: October 30, 2006

M2:20820525.01

BIOLOGY

Fifth Edition

CAMPBELL
REECE MITCHELL

Publisher: Jim Green

Executive Editor: Erin Mulligan

Senior Developmental Editors: Pat Burner, Shelley Parlante

Managing Editor: Laura Kenney

Senior Production Editor: Angela Mann

Art and Design Manager: Don Kesner

Senior Art Supervisor: Donna Kalal

Principal Artists for the Fifth Edition: Karl Miyajima, Precision Graphics, Carla Simmons, Mary Ann Tenorio

Photo Researchers: Kathleen Cameron, Roberta Spieckerman

Permissions Editor: Ariane dePree-Kajfez

Text Designer/Layout Artist: Mark Ong, Side by Side Studios

Cover Designer: Yvo Riezebos

Copyeditor: Alan Titche

Proofreader: Anita Wagner

Indexer: Shane-Armstrong Information Systems

Prepress Supervisor: Vivian McDougal

Compositor: American Composition & Graphics, Inc.

Film House: H&S Graphics, Inc.

Market Development Manager: David Horwitz

Channel Marketing Manager: Gay Meixel

On the cover:
Magnolia Blossom, Tower of Jewels, 1925.
Photograph by Imogen Cunningham, ©1974 The Imogen Cunningham Trust.

Library of Congress Cataloging-in-Publication Data
Campbell, Neil A., 1946–
Biology/Neil A. Campbell, Jane B. Reece, Lawrence G. Mitchell.—5th ed.
p. cm.
Includes index.
ISBN 0-8053-6573-7
1. Biology. I. Reece, Jane B. II. Mitchell, Lawrence G. III. Title.
QH308.2.C34 1999
570—dc21 98-45707
CIP

2 3 4 5 6 7 8 9 10—VH—02 01 00 99

High School Binding distributed by
Scott Foresman-Addison Wesley
Glenview, Illinois
ISBN 0-8053-6566-4

Benjamin/Cummings, an imprint of Addison Wesley Longman, Inc.
2725 Sand Hill Road
Menlo Park, CA 94025

hydrophobic tails point toward the interior of the membrane, away from the water. The phospholipid bilayer forms a boundary between the cell and its external environment; in fact, phospholipids are major components of cell membranes. This behavior provides another example of how form fits function at the molecular level.

Steroids include cholesterol and certain hormones

Steroids are lipids characterized by a carbon skeleton consisting of four fused rings (FIGURE 5.14). Different steroids vary in the functional groups attached to this ensemble of rings. One steroid, **cholesterol**, is a common component of animal cell membranes and is also the precursor from which other steroids are synthesized. Many hormones, including vertebrate sex hormones, are steroids produced from cholesterol (see FIGURE 4.8). Thus, cholesterol is a crucial molecule in animals, although a high level of it in the blood may contribute to atherosclerosis.

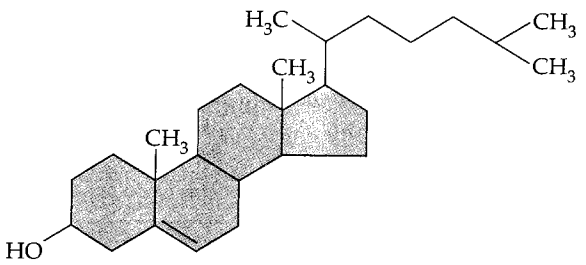

FIGURE 5.14 • Cholesterol: a steroid. Cholesterol is the molecule from which other steroids, including the sex hormones, are synthesized. Steroids vary in the functional groups attached to their four interconnected rings (shown in gold).

PROTEINS—THE MOLECULAR TOOLS OF THE CELL

5.3 The importance of proteins is implied by their name, which comes from the Greek word *proteios,* meaning "first place." **Proteins** account for more than 50% of the dry weight of most cells, and they are instrumental in almost everything organisms do (TABLE 5.1). Proteins are used for structural support, storage, transport of other substances, signaling from one part of the organism to another, movement, and defense against foreign substances. In addition, as enzymes, proteins regulate metabolism by selectively accelerating chemical reactions in the cell. A human has tens of thousands of different proteins, each with a specific structure and function.

Proteins are the most structurally sophisticated molecules known. Consistent with their diverse functions, they vary extensively in structure, each type of protein having a unique three-dimensional shape, or **conformation**. Diverse though proteins may be, they are all polymers constructed from the same set of 20 amino acids. Polymers of amino acids are called **polypeptides**. A protein consists of one or more polypeptides folded and coiled into specific conformations.

A polypeptide is a polymer of amino acids connected in a specific sequence

As mentioned in Chapter 4, **amino acids** are organic molecules possessing both carboxyl and amino groups. The figure at the right shows the general formula for an amino acid:

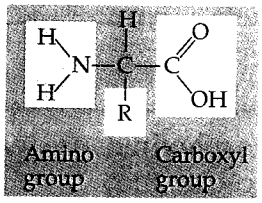

Table 5.1 An Overview of Protein Functions

TYPE OF PROTEIN	FUNCTION	EXAMPLES
Structural proteins	Support	Insects and spiders use silk fibers to make their cocoons and webs, respectively. Collagen and elastin provide a fibrous framework in animal connective tissues, such as tendons and ligaments. Keratin is the protein of hair, horns, feathers, and other skin appendages.
Storage proteins	Storage of amino acids	Ovalbumin is the protein of egg white, used as an amino acid source for the developing embryo. Casein, the protein of milk, is the major source of amino acids for baby mammals. Plants have storage proteins in their seeds.
Transport proteins	Transport of other substances	Hemoglobin, the iron-containing protein of vertebrate blood, transports oxygen from the lungs to other parts of the body. Other proteins transport molecules across cell membranes.
Hormonal proteins	Coordination of an organism's activities	Insulin, a hormone secreted by the pancreas, helps regulate the concentration of sugar in the blood of vertebrates.
Receptor proteins	Response of cell to chemical stimuli	Receptors built into the membrane of a nerve cell detect chemical signals released by other nerve cells.
Contractile proteins	Movement	Actin and myosin are responsible for the movement of muscles. Contractile proteins are responsible for the undulations of cilia and flagella, which propel many cells.
Defensive proteins	Protection against disease	Antibodies combat bacteria and viruses.
Enzymatic proteins	Selective acceleration of chemical reactions	Digestive enzymes hydrolyze the polymers in food.

At the center of the amino acid is an asymmetric carbon atom. Its four different partners are an amino group, a carboxyl group, a hydrogen atom, and a variable group symbolized by R. The R group, also called the side chain, differs with the amino acid. FIGURE 5.15 shows the 20 amino acids that cells use to build their thousands of proteins. (Here the amino and carboxyl groups are all depicted in ionized form.) The R group may be as simple as a hydrogen atom, as in the amino acid glycine (the one amino acid lacking an asymmetric carbon), or it may be a carbon skeleton with various functional

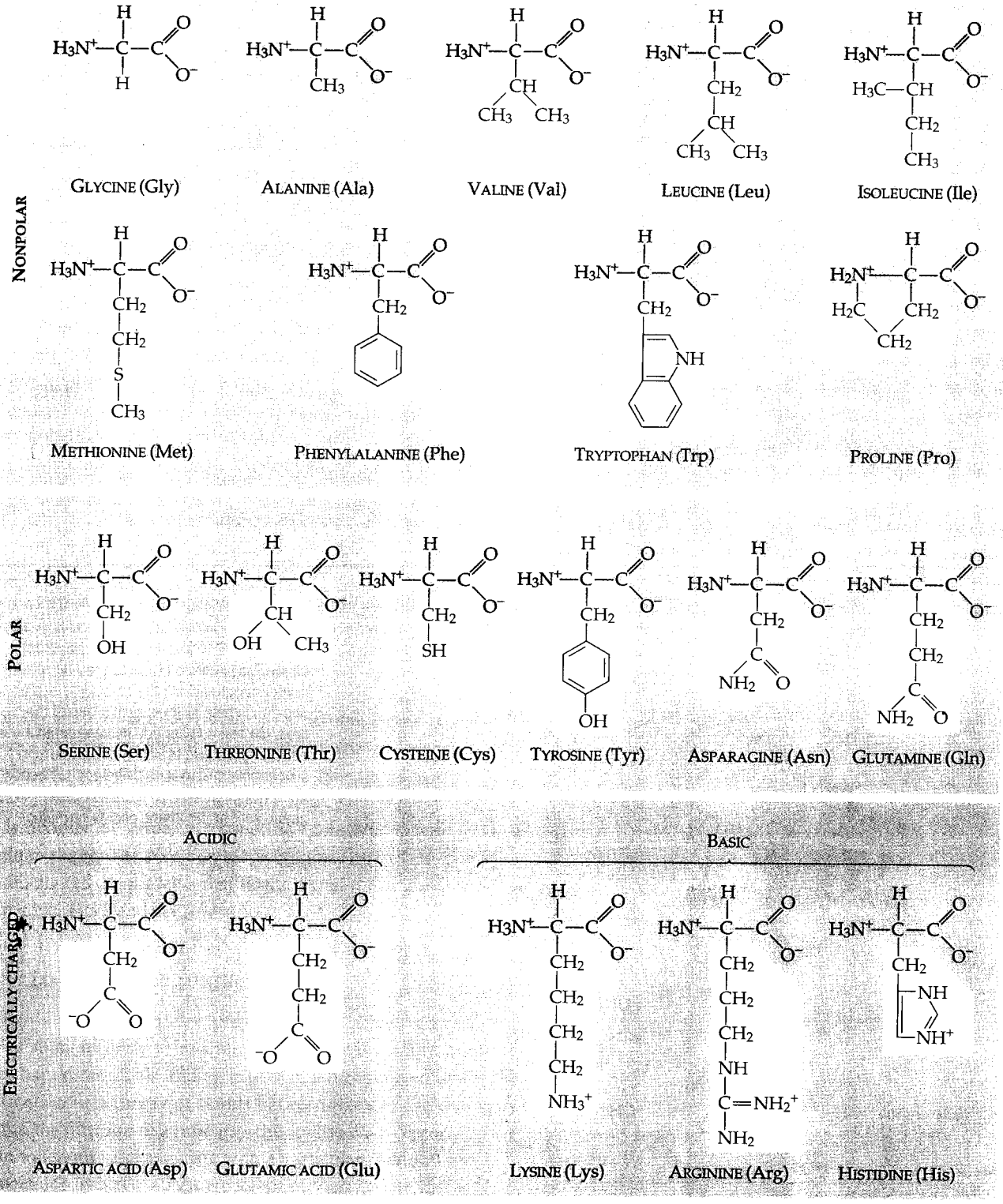

FIGURE 5.15 • The 20 amino acids of proteins. The amino acids are grouped here according to the properties of their side chains (R groups), highlighted in white. The amino acids are shown in their prevailing ionic forms at pH 7, the approximate pH within a cell. In parentheses are the three-letter abbreviations for the amino acids.